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Review

Proteomics as a new paradigm to tackle Parkinson's disease research challenges

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ABSTRACT

Disease-modifying therapies capable to stop or slow Parkinson's disease (PD) progression are still elusive due to severe shortcomings in the understanding of PD etiopathogenesis as well as limitations in routine clinically-based diagnosis precluding PD detection during its early course. Proteomics has recently emerged as one of the most attractive approaches to unravel the complex nature of PD processes and investigate PD potential biomarkers. In contrast to traditional candidate-based studies, it offers global and high-throughput strategies to systematically analyze proteins – the pathological effectors themselves – without the need to establish *a priori* hypotheses. This review aims to summarize the latest advances in PD research in the context of proteomics. After an overview of some methodological aspects, the most recent PD-related findings will be discussed together with the limitations and perspectives of current proteomic workflows.

Contents

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1. Introduction

Parkinson's disease (PD) is the most common neurodegenerative movement disorder, affecting adult individuals of all races and culture. The progressive deterioration of motor function, manifested clinically by various degrees of tremor at rest, rigidity, slowness of movement (bradykinesia) and postural instability, appears after a significant loss of dopaminergic neurons in the substantia nigra (SN) pars compacta has been reached. Nigral neurodegeneration together with the presence of distinctive intracytoplasmic inclusions referred to as Lewy bodies (LB) in the surviving neurons are the two invariant pathological hallmarks of PD which are mandatory to establish a definitive diagnosis at autopsy. Non-motor symptoms encompassing cognitive decline, anxiety, sleep disturbances, or autonomic impairment are increasingly recognized to be part of the PD clinical spectrum and may result from the vulnerability of selected neuronal populations in numerous regions of the central and autonomous nervous systems.

Altogether, PD results in major functional disabilities impacting quality of life, working capacity and life expectancy with mortality rates being nearly doubled in PD versus aged-matched subjects [1–3]. Despite the remarkable efficacy of dopamine replacement therapy to alleviate motor symptoms and improve patients' quality of life, PD remains incurable without any treatment available to modify or stop the disease's rampage through the nervous system. The estimated direct and indirect costs related to the illness ranks high among brain disorders, amounting up to 13.9 billion euros in Europe for the year 2010 alone [4]. The number of PD cases, which currently approximates 1.2 million in Europe (0.3% of the general population) and 1 million in the USA, is expected to double by year 2030 along with the increase of life expectancy in the Western populations [4–6]. In the absence of any disease-modifying therapy yet, the socioeconomic and financial burdens incurred by PD will continue to grow and defy our healthcare system over the coming decades.

Before any preventive or curative intervention could be designed, a clear and detailed understanding of the molecular mechanisms underlying neurodegeneration in sporadic PD is required. However, despite decades of research, this is definitely not the case yet. Many mechanisms have been shown to sensitize neurons to death, including impairment of protein degradation systems, mitochondrial dysfunction and oxidative stress, inflammation, excitotoxicity or enhanced apoptosis. In all likelihood, more than one of these, and possible many others, might be at work in PD but the precise combination and temporal succession of the molecular events leading to cell death remain to be disentangled.

Thus far, research into PD pathogenesis has heavily relied upon toxic and transgenic animal models, the engineering of which has derived from rare neurotoxin-induced and monogenic forms of parkinsonism in humans. However, these hypothesis-driven approaches have demonstrated major limitations, casting serious doubts about the validity of such models to address the complexity of PD pathogenesis. The recent emergence of more global, unbiased and hypothesis-free disciplines such as GWAS and "omics" may provide new research paradigms to explore PD pathogenesis and PD biomarkers, which may respectively pave the way for original neuroprotective or neuroregenerative therapeutic targets and offer early and accurate diagnostic tools. After reappraising some key aspects of PD neuropathology and etiopathogenesis, this review aims to summarize the ultimate advances in PD research in the context of proteomics. We will glance over proteomics techniques from sample preparation to mass spectrometry (MS) analysis before examining the most recent PD-related findings, limitations and future directions.

2. PD neuropathology: the disease substrates

2.1. Neuropathological hallmarks

Most available evidence suggests that the lesional core of PD pathology is the damage of dopaminergic cells in the SN pars compacta [7], which results in dopamine (DA) depletion in the striatum and destabilization of the basal ganglia (BG) motor control loops [8]. Nigral neurodegeneration is thus unambiguously linked to motor symptoms, which first become apparent when about 80% of striatal dopaminergic terminals and 50–60% of nigral dopaminergic cell bodies are already lost [9,10]. In the SN, neuronal loss is greater in the calbindin D_{28K}-poor compartments termed nigrosomes than in the calbindin D_{28K}-enriched matrix. The degree of neuronal loss is related to disease duration and follows a stereotyped spatiotemporal progression (from the more caudal nigrosome N1 > N2 > N4 > N3 to the more rostral nigrosome N5) [11] consistently observed across PD patients and differing from normal aging or other neurodegenerative disorders [7]. While neuronal loss is particularly severe within the SN ventrolateral tier, involvement of other midbrain dopaminergic cell populations (medial and medioventral, A8, substantia nigra pars lateralis, central gray substance) is less pronounced and may rather reflect some physiological aging-related decline [12].

Surviving nigral neurons frequently exhibit cytoplasmic protein inclusions referred to as LB or Lewy neurites if located in neuronal processes, which contain, among many others proteins, misfolded α-synuclein (α-SYN) and ubiquitin (Ub) [13]. It is still unclear if LBs themselves are the pathological entities interfering with normal cell function, if they represent a cytoprotective mechanism similarly to aggresomes or a failed attempt to eliminate cytotoxic proteins such as misfolded α-SYN. The percentage of LB-bearing nigral cells appears to be stable over time (3.6% in average), suggesting that they are eliminated as the disease progresses when the afflicted neurons die. Thus, in the SN at least, LB may be closely related to nigral neuronal loss [14]. Current knowledge on LB structure, formation, composition and role in cell death is still limited and reviewed elsewhere (in [15]). Of note, LBs are not specific for PD, as they are found in other forms of parkinsonism collectively termed "synucleopathies" (i.e., dementia with LB, multiple system atrophy), in Alzheimer's disease (AD), as well as incidentally in aged people [16].

2.2. Extranigral aspects of PD and Braak staging

Neuronal loss and LB formation are neither confined to the midbrain and the SN, nor restricted to the dopaminergic neurochemical system. Based on neuropathological studies, PD is now rather viewed as a multisystem disorder affecting numerous neuronal populations both in the central and peripheral nervous systems [17]. Dopaminergic neurons found outside the midbrain are unequally vulnerable to PD, partially lost in the retina [18] and enteric nervous system [19] while relatively spared in the